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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,230	PRUSINER, STANLEY B.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-28 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-28 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6/02 8/01
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-28 are pending in the instant application.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The specification is completely lacking in antecedent basis for the claims directed to dog, cat, goat, or turkey prion preparations or methods of making them. Claims 8, 14, and 19 are directed to dog, cat, goat, or turkey prion preparations or methods of making them wherein dog, cat, goat, or turkey prions are propagated in a transgenic mouse. The specification does not contemplate prion preparations comprising dog, cat, goat, or turkey prions. The specification does not specifically contemplate methods of making dog, cat, goat, or turkey prions. Furthermore, the specification does not contemplate transgenic mice that can be used to propagate dog, cat, goat, or turkey prions.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the

conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,908,969. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of pending Claims 17-19 encompass the method of Claims 1-6 of the patent wherein a prion preparation is made from a plurality of transgenic mice each having an ablated endogenous PrP gene and an exogenous PrP gene. Claims 17-19 are directed to a method of making a prion preparation from a plurality of transgenic host animals having an ablated endogenous PrP gene, wherein the host animal is genetically manipulated to allow infection by prions that normally only infect a genetically diverse animal.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a prion preparation obtained from the brain of a transgenic mouse comprising a genome wherein both alleles of the mouse endogenous PrP gene are ablated and an exogenous human, bovine, or Syrian hamster PrP transgene is operatively inserted, and wherein the preparation comprises infectious prions (a) that cause disease in a known species of mammal, (b) which are of a known strain, and (c) which are present in a known amount, does not reasonably provide enablement for a prion preparation of the type claimed wherein the prions are obtained from any animal. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a standardized prion preparation comprising prions obtained from a plurality of animals and a carrier, wherein the preparation comprises prions which infect and cause disease in a known species of animal, which are of a known strain, and which are present in a known amount, and further wherein the carrier is of a known composition which is different from brain tissue of the mammal which the prions would infect in the animals natural state.

The specification fails to provide an enabling disclosure for the claimed prion preparation because the specification does not teach how to propagate prions from one species of animal in any other genetically diverse species of animal other than in the brain of the transgenic mouse of the type described in the specification wherein both alleles of the endogenous murine PrP gene are ablated and an exogenous mammalian PrP transgene is operatively inserted. The claims encompass prion preparations isolated from any species of animal, transgenic or non-transgenic, but the specification does not teach how to obtain prions appropriate for the claimed preparation from anything other than transgenic mice of the type indicated above.

The specification fails to provide an enabling disclosure for the claimed prion preparation because the specification does not teach how to propagate and obtain prions from any tissue other than the brain. The claims encompass prion preparations isolated from the blood or any other tissue of any animal. For example, the claims encompass bovine prion preparations isolated from the blood of cows, mice, or any other animal, transgenic or non-transgenic, but the specification does not teach how to propagate bovine prions in the blood of cows, mice, or any other animal. The specification only teaches how to obtain prions appropriate for the claimed preparation from the brain of a transgenic mouse. Thus, the claims are enabled only for prion preparations obtained from the brain of a transgenic mouse of the type indicated above.

With regard to Claim 3, the specification fails to provide an enabling disclosure for the claimed prion preparation because the specification does not teach how to infect a non-transgenic mouse with human, cow, or sheep prions. Accordingly, the specification does not teach how to propagate human, cow, or sheep prions in any type of mouse other than a transgenic mouse of the genotype Tg(HuPrP)/Prnp$^{0/0}$, Tg(BovPrP)/Prnp$^{0/0}$, and Tg(ShePrP)/Prnp$^{0/0}$, respectively. The claim encompasses human, cow, and sheep prion preparations obtained from the brain of a non-transgenic mouse, wherein the human, cow, and sheep prions were propagated in the brain of the non-transgenic mouse, but the specification does not teach how to accomplish this.

The specification fails to provide an enabling disclosure for the claimed prion preparation wherein the prions are obtained from any species of animal because the specification does not teach how to prepare any species of transgenic animal appropriate for propagation and isolation of exogenous prions other than the transgenic mouse of the type indicated above. The claims encompass prion preparations isolated from any species of transgenic animal, but the specification does not teach how to obtain prions appropriate for the claimed preparation from anything other than transgenic mice of the type indicated above.

Accordingly, the specification fails to provide an enabling disclosure for the preparation of any and all species of transgenic animals appropriate for the propagation and isolation of exogenous prions because the phenotype of a transgenic animal cannot be predicted. While the specification discloses transgenic mice wherein both alleles of the endogenous PrP gene have been ablated and an exogenous PrP gene is introduced into the genome, and wherein the mice exhibit an enhanced susceptibility to infection by a prion from a divergent source when compared to non-transgenic mice, the phenotype of any other species of host animal harboring a similar transgene construct comprising a PrP gene from any species, cannot be predicted. The specification does not teach what phenotype would be expected in any species of transgenic animal, other than a mouse. No guidance is provided with respect to how one would have prepared any transgenic animals exhibiting any transgene-dependent phenotypic alteration, other than

mice. The mere capability to perform gene transfer in any given species is not enabling for the requisite transgenic animals because the desired phenotype cannot be predictably achieved simply by introducing transgene constructs of the same type as or analogous to those used to produce the PrP transgenic mice. While gene transfer techniques are well-developed for a number of species, especially the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a mouse will not necessarily achieve the same result in a rat. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). This is especially relevant for species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic animals. Furthermore, there are inherent physiological differences between mice, rabbits, guinea pigs, etc. that can affect the phenotype in an unpredictable manner. With the limited working examples, the existence of any phenotypic alteration resulting from the introduction of an exogenous PrP gene in conjuction with an ablated endogenous PrP gene in any species of animal, other than the mouse, is highly unpredictable. Given the limited guidance in the specification, the limited working examples and the unpredictability in the art, one of ordinary skill

in the art would have been required to engage in undue experimentation in order to make and use appropriate transgenic animals of any species other than the mouse.

While the species-specific requirements for transgene design are not clearly understood, examples in the literature demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Hammer et al., 1990 describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. This study was preceded by the failure to develop human disease-like symptoms in transgenic mice expressing the same transgenes that successfully caused the desired symptoms in transgenic rats (p. 1099, column 2, paragraph 2).

The specification fails to provide an enabling disclosure for the preparation of any and all transgenic host animals of the type required because the species barrier, discussed in U.S. Patent No. 5,792,901 (column 14, lines 1-10), makes it difficult to predict whether introduction of a specific PrP transgene (of any species origin) into a particular host (any animal) will render the host susceptible to infection with prions obtained from the species that is the source of the exogenously introduced PrP transgene. For example, it is not readily apparent that a hamster with an ablated endogenous PrP gene and a turkey PrP transgene would be susceptible to infection with a turkey prion. Furthermore, the sequence of the turkey prion is not disclosed in the instant specification. Thus, the specification does not teach how to make a transgenic animal harboring a turkey PrP gene. The specification reveals on pages 25-26 that the DNA sequences of the human, sheep, cow, and chicken PrP genes have been determined. However, the turkey PrP gene is not disclosed.

The specification fails to provide an enabling disclosure for prion preparations of the type claimed comprising dog, cat, turkey, chicken, goat, or sheep prions because appropriate transgenic animals are not disclosed and are not available. As discussed above, the phenotype of a transgenic animal

cannot be predicted. Furthermore, the specification does not teach or point to a reference that teaches the nucleotide sequence of the dog, cat, turkey, and goat PrP genes. Thus, the specification does not teach how to make any transgenic animal harboring a dog, cat, turkey, or goat PrP gene and, consequently, sources appropriate for isolation of the claimed prion preparations are not available and no guidance is offered for any other method of obtaining the claimed prion preparations comprising dog, cat, turkey, and goat prions

The specification fails to provide an enabling disclosure for the claimed prion preparations obtained from a transgenic animal or transgenic mouse with an exogenous PrP transgene and with a single endogenous PrP allele ablated or with neither allele ablated because the specification teaches that when transgenic mice are made in accordance with the invention, both alleles of the endogenous PrP gene must be ablated in order for the mice to become susceptible to infection with a prion from the species that is the source of the exogenous PrP gene (see, e.g., column 31, Example 8 of U.S. Patent No. 5,792,901). For example, Tg(HuPrP) mice are resistant to infection with human prions.

With regard to Claim 9, the specification fails to provide an enabling disclosure for obtaining prions from Tg(HuPrP), Tg(HuPrP)/Prnp$^{+/0}$, Tg(HuPrP^{CJD}), Tg(HuPrP^{CJD})/Prnp$^{+/0}$, Tg(ShePrP), Tg(ShePrP)/Prnp$^{+/0}$, Tg(ShePrP)/Prnp$^{0/0}$, Tg(BovPrP), Tg(BovPrP)/Prnp$^{+/0}$ mice for the reasons discussed in the preceding paragraph. The prion preparations obtained from sheep PrP transgenic mice are not enabled because sheep PrP transgenic mice are not disclosed and, as discussed above, the phenotype of a transgenic animal cannot be predicted.

With regard to Claim 8, the specification fails to provide an enabling disclosure for the claimed prion preparations wherein cow, sheep, dog, cat, goat, chicken, or tukey prions are produced in a transgenic mouse because the specification does not teach how to make a transgenic mouse with a chimeric transgene that can be infected with a cow, sheep, dog, cat, goat, chicken, or turkey prion.

Claims 11-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a prion protein standard comprising isolated exogenous prions from a plurality of transgenic mice each comprising a genome wherein both alleles of the murine endogenous PrP gene are ablated and an exogenous human, bovine, or Syrian hamster PrP transgene is operatively inserted, and wherein the standard further comprises brain homogenate from the animal that is the source of the exogenous PrP gene, does not reasonably provide enablement for a prion protein standard comprising isolated exogenous prions from a plurality of transgenic mice genetically manipulated to allow infection by prions that normally only infect a genetically diverse animal and further comprising brain homogenate from the genetically diverse animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification fails to provide an enabling disclosure for the claimed prion protein standard for the reasons discussed above regarding the scope of enablement of the transgenic mice that are appropriate for the isolation of exogenous prions.

The specification fails to provide an enabling disclosure for the claimed prion protein standard comprising exogenous prions isolated from any transgenic mouse produced by any genetic manipulation that permits infection by exogenous prions because the specification does not disclose any method for rendering a mouse susceptible to infection by exogenous prions other than by ablating both alleles of the endogenous murine PrP gene and inserting an exogenous PrP gene derived from another species of animal. The claims encompass any genetic manipulation that renders the mouse susceptible to infection by exogenous prions, but the specification is enabling for only one genetic strategy to produce susceptible mice.

With regard to Claim 14, the specification fails to provide an enabling disclosure for the prion protein standard wherein the prions are isolated from a transgenic mouse genetically manipulated to allow for infection by sheep, dog, cat, goat, chicken, or turkey prions because transgenic mice harboring sheep,

dog, cat, goat, chicken, or turkey PrP genes are not disclosed and the specification does not offer any guidance for any other genetic manipulation that would render the transgenic mouse susceptible to infection by prions from sheep, dog, cat, goat, chicken, or turkey. Furthermore, as discussed above, the phenotype of a transgenic animal cannot be predicted.

Claims 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for preparing a prion protein standard from a plurality of transgenic mice having an ablated endogenous PrP gene and an exogenous human, bovine, or Syrian hamster PrP gene operatively inserted wherein the mice are rendered susceptible to infection by prions that normally only infect a genetically diverse mammal, does not reasonably provide enablement for a method for preparing a prion protein standard from any transgenic host animal having an ablated endogenous gene wherein the host animal comprises any genetic modification that allows infection by prions that normally only infect a genetically diverse animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification fails to provide an enabling disclosure for the claimed method because the specification is not enabling for all transgenic host animals nor for any genetic modification for the reasons discussed above.

With regard to Claim 19, the specification fails to provide an enabling disclosure for the claimed method wherein the prion protein standard is prepared from transgenic mice that are susceptible to infection by sheep, dog, cat, goat, chicken, or turkey prions. The specification does not disclose transgenic mice that are susceptible to infection by sheep, dog, cat, goat, chicken, or turkey prions and no guidance is offered for making the appropriate mice. Furthermore, for the reasons discussed above, the phenotype of any transgenic animal cannot be predicted.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-22 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-10 are indefinite because the claims recite that "the carrier is of a known composition which is different from brain tissue of the mammal which the prions would infect in the animals natural state." The specification clearly contemplates using brain homogenates to make the prion preparation. However, brain tissue is not of a known composition. For the preparation to be of a known composition, the identity and concentration of each component must be known.

Claims 1-10, 17, and 27 are indefinite in their recitation of the phrase "characterized by" because it is unclear whether mere description or an actual physical characterization step is intended. Use of standard language such as "comprises," "consists of," "wherein," etc. is suggested.

Claim 2 is indefinite in the recitation of "wherein the known amount is a known number of infectious units and known concentration" because an "amount" is not a "concentration."

Claims 3 and 4 are indefinite in their recitation of "comprised of" because it is unclear whether this is intended as open or closed claim language. Use of "comprises" or "consists of" is suggested.

Claim 4 is indefinite in its recitation of "substantially all" because it is unclear what is meant by this term.

Claim 8 is indefinite with regard to the "groups consisting of" because this claim language is improper Markush terminology. "Groups" should not be in the plural form.

Claims 8, 14, and 19 uses improper Markush terminology because "or" should be "and."

Claims 11-16 are indefinite in their recitation of the standard with "properties sufficiently established to serve as reference control for prion measurement protocols" because it is unclear what properties would be required or considered sufficient.

Claim 13 is indefinite with regard to "a known genetic homogeneity" because it is unclear what is meant by this term.

Claim 14 is indefinite because "the transgenic host mammal" lacks antecedent basis in Claim 11.

Claim 15 is indefinite because it is unclear how the prions from the first plurality of mice are separate from the prions from the second plurality of mice when the standard of Claim 11 "further comprises" exogenous prions from a second plurality of transgenic mice.

Claims 20-22 are indefinite in their recitation of "a true value" because the specification does not offer any guidance for determining a "true value." The specification defines the "true value" as the level of prion protein present in a sample that is detectable using reliable techniques known in the art for determining protein levels (p. 18, paragraph 0059), but the specification does not offer any guidance as to which techniques would be considered reliable enough to render a "true value."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 7, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Scott et al. (1989).

The claims are directed to a standardized prion preparation comprising prions obtained from a plurality of animals and a carrier, wherein the preparation comprises prions which infect and cause disease in a known species of animal, which are of a known strain, and which are present in a known amount, and further wherein the carrier is of a known composition which is different from brain tissue of the mammal which the prions would infect in the animals natural state.

Scott et al. (1989) disclose prion protein preparations made from transgenic mice carrying the Syrian hamster (SHa) prion protein gene. Three Tg 81 mice that developed clinical scrapie after inoculation with Syrian hamster prions were sacrificed and their brains were bioassayed for scrapie infectivity in hamsters and mice. Weanling hamsters inoculated with a 10-fold dilution of a 10% (w/v) homogenate of Tg 81 mouse (Mo) brain developed clinical signs of scrapie in about 75 days and died almost 2 weeks later. These incubation times are similar to those observed when homogenates of SHa brains containing approx. 10^9 ID_{50} U of prions per gram of brain were assayed in hamsters. Tg 81 brains contained approximately 10^9 ID_{50} units of SHa prions based on SHa bioassays (abstract). Since Tg 81 mice are capable of synthesizing both SHa and Mo prions, inocula prepared from the Tg 81 brains were injected into Swiss CD-1 mice to determine whether infectious Mo prions were present. None of the Swiss CD-1 mice developed scrapie. A mixture of SHa and Mo prions inoculated into Syrian hamsters and Swiss CD-1 mice produced scrapie in both species with incubation times similar to those observed when SHa and Mo prions were inoculated separately (p. 851, column 2, paragraph 2). Thus, the data indicate that infectious Mo prions are not produced in the brains of Tg 81 mice. Therefore, the prion preparation described contains only prions of a single strain, the SHa prions.

Claims 1, 4, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Caughey et al. (1988).

The claims are directed to a standardized prion preparation comprising prions obtained from a plurality of animals and a carrier, wherein the preparation comprises prions which infect and cause disease in a known species of animal, which are of a known strain, and which are present in a known amount, and further wherein the carrier is of a known composition which is different from brain tissue of the mammal which the prions would infect in the animals natural state. The claims indicate that the prions are obtained from a plurality of animals, or 10 or more animals (Claim 7), or a transgenic mouse (Claim 7). However, the claims are directed to a preparation of a particular composition that does not

depend on the source from which the prions are obtained. Determination of patentability is based on the product itself. See MPEP 2113. Thus, the prions do not have to be obtained from an animal to make the claimed product. The patentability of the product does not depend on its method of production.

Caughey et al. (1988) disclose the preparation of PrP uncontaminated by scrapie-infected tissue. Murine PrP cDNA cloned from a scrapie-infected mouse brain was expressed in mouse C127 cells *in vitro*. The expressed polypeptides appeared to be glycosylated and were released from the cell surface into the medium. The expressed PrP was further purified by immunoprecipitation using anti-PrP peptide serum 783 (p. 4657, column 2, paragraph 2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scott et al. (1989).

Claims 20-22 are directed to a method of calibration of a prion protein assay. Claims 23-28 are directed to a prion protein standard kit.

Scott et al. (1989) disclose prion protein preparations made from transgenic mice carrying the Syrian hamster (SHa) prion protein gene, as discussed above. SHa bioassays revealed the Tg 81 brains contained approximately 10^9 ID_{50} units of SHa prions.

Since the methods presented require only an appropriate prion preparation and standard scientific methodology, one skilled in the art would have been motivated to use the prion preparations disclosed by Scott et al. to compare different prion protein detection assay methods to determine which assay methods were the most reliable or to develop improved assay methods that are either more precise or more accurate or both. One skilled in the art would have anticipated a reasonable expectation of success

because appropriate prion preparations as disclosed by Scott et al. were available and only standard scientific methodology is additionally required to calibrate an assay. One skilled in the art would have been motivated to put together the claimed prion protein standard kit to make available conveniently aliquoted standards of a variety of prion strains in a series of dilutions appropriate for the construction of a standard curve for any assay. One skilled in the art would have anticipated a reasonable expectation of success because the claimed kits can be easily assembled by simply determining what standards are needed to perform an analysis.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Closest Prior Art

Gabriel et al., 1992 disclose the amino acid sequence of several PrP proteins from various of species, including bovine, sheep, and mouse. Goldmann et al., 1991 disclose the sequence of the bovine PrP gene. Westaway et al., 1994 disclose the sequence of the sheep PrP gene. Locht et al., 1986 disclose the sequence of the mouse PrP gene. Kretzschmar et al., 1986 disclose the sequence of the human PrP gene. Bueler et al., 1992 generated mice homozygous for disrupted PrP genes and demonstrated that the mice developed normally, thereby suggesting the expendability of the PrP protein. The prior art does not disclose or fairly suggest propagating exogenous prions in the brains of transgenic mice of the type disclosed, and using the brain tissue from the mice to make a prion preparation that can serve as a reference material or standard.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Friday from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips whose telephone number is (703) 305-3482.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER